REMARKS

I. Status Summary

Claims 1-25 previously were pending in the instant U.S. patent application. Claims 1-25 were subjected to a Restriction/Election Requirement. The Examiner has acknowledged Applicants' election of Claims 1-7 and 24-25 and the cancellation of non-elected Claims 8-23. As a result, Claims 1-7 and 24-25 are pending in the instant application and have been examined. Claims 1-7 and 24-25 presently stand rejected. Claims 1, 5, and 24 are amended by the present Amendment. New Claims 26-31 are added by the present Amendment. Therefore, upon entry of Amendment A, Claims 1-7 and 24-31 will remain pending in the instant patent application.

II. Applicants' Voluntary Amendment of Claim 24

Applicants have amended Claim 24 by a way of a clarifying, non-limiting amendment to more particularly point out the claimed subject matter. More specifically, Applicants have amended Claim 24 by striking the reference to Claim 1, thereby removing the dependency of Claim 24 from Claim 1. As a result, Applicants note that amended Claim 24 is now an independent claim. Support for this amendment can be found in Claim 24 and Claim 1 as filed. Claim 24 as filed recited a contrast enhancement agent comprising the same elements as recited in Claim 1 as filed. Thus, Applicants respectfully submit that it is not necessary for Claim 24 to be dependent from Claim 1. Accordingly, Applicants respectfully submit that Claim 24 is now in condition for allowance and respectfully request the same. No new matter has been added.

III. Response to Claim Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claims 1-7 and 24-25 under 35 U.S.C. § 112, first paragraph, under the contention that they fail to comply with the enablement requirement set forth therein. The bases for these rejections are presented on pages 2-4 of the Official Action. After careful consideration of these rejections and the

Examiner's bases therefor, Applicants respectfully traverse these rejections and submit the following Remarks.

Applicants initially submit that as a matter of Patent Office practice, the burden rests upon the Examiner to establish a prima facie case of a failure to comply with 35 U.S.C. § 112, first paragraph, with respect to the subject matter described and claimed in Applicants' patent application. See In re Marzocchi, 58 C.C.P.A. 1069, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971). Applicants respectfully submit that the Examiner has not met the burden of establishing a prima facie case of a failure to comply with 35 U.S.C. §112, first paragraph, and traverse the Examiner's rejection of Claims 1-7 and 24-25 under 35 U.S.C. § 112, first paragraph, as follows.

The Examiner contends that the claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Official Action, page 2, third paragraph. Applicants submit, however, that the Examiner has not presented, as is required under In re Marzocchi, evidence or reasons why the specification does not enable the subject matter recited in the claims. Instead, the Examiner has offered only a series of conclusory statements contending that the specification of the instant patent application does not adequately enable one of ordinary skill in the art to use metal complexes with the claimed peptide sequences as contrast enhancement agents. For example, the Examiner contends that there is no predictability regarding the use of any metal ion-chelator (MC) complex with the claimed sequence regarding stereo-hindrance. Official Action, page 3, third paragraph. The Examiner, however, has offered no specific scientific or other factual basis in support of this contention. Indeed, the Examiner has cited no patents, no journal articles, and no other scientific literature or other information in support of this position.

Applicants submit that 35 U.S.C. § 112, first paragraph, requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. See Wang Labs. v. Toshiba Corp., 993

F.2d 858, 865 (Fed. Cir. 1993). Applicants respectfully submit that this requirement has been met.

Accordingly, Applicants respectfully submit that a prima facie case of a failure to comply with 35 U.S.C. § 112, first paragraph, has not been made. Therefore, Claim 1 and Claim 24 are believed to be in compliance with 35 U.S.C. § 112, first paragraph. Claims 2-7 and 25 ultimately depend upon Claim 1 and Claim 24, respectively. In the absence of specific bases for the rejection of these claims in the Official Action, Claims 2-7 and 25 also are believed to comply with the requirements of 35 U.S.C. §112, first paragraph. Therefore, Applicants respectfully request that the Examiner's rejection of Claims 1-7 and 24-25 under 35 U.S.C. § 112, first paragraph, be withdrawn, and Claims 1-7 and 24-25 be allowed at this time.

Assuming arguendo, however, that the Examiner has made a prima facie case of a failure to comply with 35 U.S.C. §112, first paragraph, Applicants respectfully submit the following. The Examiner's primary contention in support of the rejection of Claims 1-7 and 24-25 under 35 U.S.C. §112, first paragraph, appears to be that undue experimentation would be required to use the entire scope of the claimed subject matter. See Official Action, page 4. Applicants respectfully submit that the Examiner has adopted an improper basis for a rejection under 35 U.S.C. § 112, first paragraph, and offer the following Remarks.

Applicants submit that the appropriate standard for measuring enablement under 35 U.S.C. §112, first paragraph, is that the claimed subject matter must be enabled so that a person skilled in the art can make and use the invention from the disclosures of the specification, coupled with information known in the art, without "undue experimentation." In re Wands, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988). Further, the quantity of experimentation to be performed by one of ordinary skill in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 195 U.S.P.Q. 150, 153 (C.C.P.A. 1977). "The test is not merely quantitative, since a considerable

amount of experimentation is permissible, if it is merely routine, or if the U.S. patent application in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed." In re Wands, 8 U.S.P.Q.2d at 1404 (citing In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. U.S. v. Telectonics, Inc., 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989). Further, Applicants further note that the level of skill in this art is high. As noted in In re Wands, this factor also must be considered in evaluating compliance with 35 U.S.C. § 112, first paragraph. Specific comments presented by the Examiner in view of the appropriate standard for measuring enablement under 35 U.S.C. §112, first paragraph, are addressed as follows.

The Examiner contends that detailed guidance regarding the making of a contrast enhancement agent comprising the peptide sequence of SEQ ID NO: 1 and an MC complex is absent from the instant application. Official Action, page 4, first paragraph. The Examiner also contends that the specification contains only a vague prophetic list of how one could make the claimed contrast enhancement agents. Official Action, page 4, first paragraph.

Turning now to the guidance provided in the disclosure of the instant application as filed, Applicants note that the design and preparation of contrast enhancement agents according to the claimed subject matter are described on pages 32-36 of the application as filed. More particularly, a method for generating a complex comprising an amino acid sequence of NXEQVSP (SEQ ID NO: 1) and an MC complex is provided in detail on pages 35-36 of the application as filed. Thus, one of ordinary skill in the art can use this guidance to prepare contrast enhancement agents in accordance with the subject matter claimed in the instant application which comprise the peptide sequence NXEQVSP (SEQ ID NO: 1), at least one paramagnetic ion, and at least one chelator as recited in independent Claims 1 and 24. Thus, Applicants respectfully submit that the guidance supplied in the instant application would enable one of skill in the art to practice the claimed subject matter without undue experimentation.

The Examiner also contends that there are no specific examples for making the claimed agents and that there are no demonstrations as how to select an adequate MC for a given peptide sequence comprising SEQ ID NO: 1 that would lead one of ordinary skill away from undue experimentation regarding possible stereo-hindrances, because it is not disclosed as to how the various MC's would be associated with the given sequence of SEQ ID NO: 1. Official Action, page 4, first paragraph. For example, the Examiner inquires whether there is an ionic association or a covalent association or through which amino acid residue the MC is associating. Official Action, page 4, first paragraph. Accordingly, the Examiner asserts that the disclosure fails to establish that any amino acid would work at the X residue position with just any of the various MC's possible. Further, the Examiner asserts that the disclosure does not demonstrate which amino acid residue in SEQ ID NO: 1 would interact with the MC and whether the association would be affected by any of the many amino acids that could be at the X residue position. Official Action, page 4, first paragraph.

Applicants submit that the Examiner appears to have adopted the position that 35 U.S.C. §112, first paragraph, requires the presentation of working examples with respect to all different combinations of metal complexes and amino acid sequences comprising NXEQVSP (SEQ ID NO: 1). Applicants respectfully note that while the presence or absence of working examples is one consideration in the overall evaluation of enablement, working examples are not required under 35 U.S.C. §112, first paragraph, to comply with the enablement standard presented therein. Indeed, the Manual of Patent Examining Procedure (hereinafter the "MPEP") states that the specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. MPEP § 2164.02. The MPEP also states that a lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement. Id. (emphasis added).

Applicants submit, however, that one of ordinary skill in the art could practice the subject matter claimed in the instant application without ascertaining the binding mechanism between the metal complex and the peptide. That is, the peptide-metal ion complexes disclosed and claimed in the instant application function as contrast enhancement agents regardless of whether the amino acid residue is covalently or non-covalently bound to the metal complex. Applicants therefore respectfully submit that the Examiner is attempting to read a requirement into the claims without any basis. Further, the application as filed provides adequate guidance for one of ordinary skill in the art for assessing candidate contrast enhancement agents. See Sections VI-VII, on pages 46-52 of the application as filed.

Applicants further submit that the application as filed describes methods for synthesizing, evaluating and characterizing candidate peptide-based contrast enhancement agents. See pages 36-41 of the application as filed. Applicants therefore respectfully submit that the specification as filed, when viewed in conjunction with information known in the art as required under the standard articulated in In re Wands, provides adequate guidance to one of ordinary skill in the art to make and use the claimed contrast enhancement agents.

Summarily, Applicants respectfully submit that the instant patent application provides adequate guidance and instruction such that one having ordinary skill in the art can make and use the subject matter claimed in pending Claims 1-7 and 24-25. Indeed, applicants respectfully submit that 35 U.S.C. §112, first paragraph, requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate in the scope of the claims, and this requirement has been met. Accordingly, Claims 1-7 and 24-25 are believed to be in compliance with 35 U.S.C. § 112, first paragraph. Thus, Applicants respectfully request that the rejection of Claims 1-7 and 24-25 under 35 U.S.C. § 112, first paragraph, be withdrawn, and that Claims 1-7 and 24-25 be allowed at this time.

IV. Response to Claim Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 1-7 and 24-25 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Official Action, page 5, second paragraph. More particularly, the Examiner asserts that Claim 1 and Claim 24 are indefinite wherein it is unclear if "X" can be any natural amino acid or can be any natural and unnatural amino acid. Official Action, page 5, third paragraph. Further, the Examiner asserts that it is unclear if "X" can be an amino acid, at least one paramagnetic metal ion and at least one chelator, or if "X" can only be an amino acid. Official Action, page 5, third paragraph. Accordingly, the Examiner suggests that the wording of the claims should be amended to clearly indicate that the agent comprises SEQ ID NO: 1, at least one paramagnetic metal ion and at least one chelator, and that "X" of SEQ ID NO: 1 can be any natural amino acid. Official Action, page 5, third paragraph.

In response to the Examiner's comments, by way of a clarifying, non-limiting amendment, Applicants amended Claim 1 by delineating the elements of "at least one peptide comprising the amino acid sequence NXEQVSP (SEQ ID NO: 1), wherein X is an amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine," "at least one paramagnetic metal ion," and "at least one chelator" into subparagraphs (a)-(c), respectively. Support for this amendment can be found in Claim 1 as filed and in the subject U.S. patent application as filed at page 3, lines 5-26.

Applicants also made a clarifying, non-limiting amendment to Claim 24 by delineating the claim elements of subparagraph (a) into subparagraphs (i)-(iii), respectively. Support for this amendment can be found in Claim 24 as filed. No new matter has been added.

In response to the Examiner's comments, Applicants further submit that one of ordinary skill in the art would recognize that the term "amino acid" is known in the art to

include natural amino acids and unnatural amino acids. Applicants further submit that the Examiner has offered no reason to presume that the term "amino acid" is or must be limited to either natural or unnatural amino acids. Therefore, Applicants respectfully submit that the Examiner is attempting to read a limitation into the claims without any basis. Accordingly, Applicants submit that Claim 1 and Claim 24 meet the requirements of 35 U.S.C. § 112, second paragraph, with respect to the term "amino acid" and respectfully request that the Examiner's rejection of Claim 1 and Claim 24 be withdrawn.

Applicants respectfully submit that the Examiner's rejections of Claim 1 and Claim 24 have been addressed and respectfully request that the Examiner's rejections of Claim 1 and Claim 24 under 35 U.S.C. § 112, second paragraph, be withdrawn and Claim 1 and Claim 24 be allowed at this time. Applicants note that Claims 2-7 and 25 are rejected for depending from rejected Claim 1 and Claim 24, respectively. Because Claim 1 and Claim 24 are now allowable, Applicants submit that dependent Claims 2-7 and 25 also are allowable and respectfully request that the Examiner's rejections of Claims 2-7 and 25 under 35 U.S.C. § 112, second paragraph, be withdrawn and Claims 2-7 and 25 be allowed at this time.

V. Response to Claim Rejections under 35 U.S.C. § 102(b)

The Examiner has rejected Claims 1-5 under 35 U.S.C. § 102(b) as being anticipated by published PCT International Patent Application No. WO/99/60018 to Storey et al. Official Action, page 5, sixth paragraph. The Examiner asserts that at pages 16-17, Storey et al. teaches peptides comprising sequences that read on the present SEQ ID NO: 1, wherein the peptides are to be associated with an MC that comprises: (a) the presently claimed paramagnetic metal ions (see page 7, lines 5-26) and (b) the presently claimed chelating compounds (see page 7, lines 27-30, and page 8, lines 1-30). Official Action, page 5, sixth paragraph. Accordingly, the Examiner asserts that Storey et al. is deemed to anticipate Claims 1-5 as drafted. Official Action, page 6, first paragraph.

In response to the Examiner's comments, Applicants amended Claim 1 by replacing the term "any," which modifies the term "amino acid," with the term "an" and inserting the phrase "selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine." Applicants also amended Claim 5 by striking reference to NQEQVSP (SEQ ID NO: 2) in the definition of the amino acid sequence and inserting the phrase "NXEQVSP (SEQ ID NO: 1), wherein X is selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine." Support for these amendments can be found throughout the specification and claims as filed, which disclose that the variable "X" in the amino acid sequence NXEQVSP (SEQ ID NO: 1) can be "any amino acid." Applicants submit that the present amendments to Claim 1 and Claim 5 merely define "X" to be one of the listed amino acids, each of which can be found listed in the subject U.S. patent application as filed at page 3, lines 5-26. In sum, Applicants submit that the amino acid sequences recited in amended Claims 1 and 5 are not taught by Storey et al.

Accordingly, Applicants submit that the Examiner's rejection of Claims 1-5 under 35 U.S.C. § 102(b) has been addressed. Therefore, Applicants respectfully request that the Examiner's rejection of Claims 1-5 under 35 U.S.C. § 102(b) be withdrawn and Claims 1-5 be allowed at this time.

VI. New Claims

Applicants added new Claims 26-31. Preliminarily, Applicants note that new Claims 26-31 are based on original Claims 1-5, and 7, and are specifically directed to contrast enhancement agents comprising a peptide consisting of the amino acid sequence NXEQVSP (SEQ ID NO: 1), wherein X is any amino acid. Applicants submit that by defining the peptide of new Claim 26 and new Claim 30 to consist only of the seven amino acid sequence NXEQVSP, new Claims 26-31 are patentably

distinguishable over the Storey et al. reference cited by the Examiner for the reasons discussed hereinabove.

More particularly, New Claim 26 recites a contrast enhancement agent useful for providing a visible image of a biological sample comprising (a) a peptide consisting of the amino acid sequence NXEQVSP (SEQ ID NO: 1), wherein X is any amino acid; (b) at least one paramagnetic metal ion; and (c) at least one chelator. Support for New Claim 26 can be found on page 32, lines 13-15; page 36, lines 12-13; and page 38, lines 1-4, of the application as filed and in original Claim 1.

New Claim 27 is dependent from new Claim 26 and recites the contrast enhancement agent of Claim 26, wherein the paramagnetic metal ion is selected from the group consisting of transition, lanthanide and actinide elements. Support for new Claim 27 can be found in original Claim 2.

New Claim 28 is dependent from new Claim 27 and recites the contrast enhancement agent of new Claim 27, wherein the paramagnetic metal ion is selected from the group consisting of Gd(III), Mn(II), Cu(II), Cr(III), Fe(II), Fe(III), Co(II), Er(II), Ni(II), Eu(III) and Dy(III). Support for new Claim 28 can be found in original Claim 3.

New Claim 29 is dependent from new Claim 26 and recites the contrast enhancement agent of new claim 26, wherein the chelator is selected from the group consisting of DTPA, substituted DTPA, DOTA, substituted DOTA, EDTA, substituted EDTA, CDTA and substituted CDTA. Support for new Claim 29 can be found in original Claim 4.

New Claim 30 is dependent from new Claim 26 and recites the contrast enhancement agent of new Claim 26, wherein the peptide is the amino acid sequence NQEQVSP (SEQ ID NO: 2); the paramagnetic metal ion is gadolinium; and the chelator is DTPA. Support for new Claim 30 can be found on page 32, lines 13-15; page 36, lines 12-13; and page 38, lines 1-4, of the application as filed and in original Claim 5.

New Claim 31 is dependent from new Claim 26 and recites the contrast enhancement agent of new Claim 26, wherein the agent is in lyophilized form. Support for new Claim 31 can be found in original Claim 7.

Applicants respectfully submit that new Claims 26-31 are now in condition for allowance and respectfully request the same. No new matter has been added.

CONCLUSION

In light of the above Amendments and Remarks, it is respectfully submitted that the instant application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

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